UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,107	11/05/2001	Michael J. Hope	10173-072	7809

7590 11/05/2002

PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-2711

EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 11/05/2002 9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/992,107	Applicant(s) Hope
	Examiner Gollamudi Kishore	Art Unit 1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 20, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *23-54* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *23-54* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The request for the extension of time and amendment dated 8-20-02 are acknowledged.

Claims included in the prosecution are 23-54.

Claim Rejections - 35 USC § 112

1.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 26-34, 39- 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The parent claims 23 and 40 already recite a composition comprising liposomes which consist essentially of. This means that there is already a carrier (either a buffer or water since liposomes are formed by hydration with an aqueous medium) present in the composition. The dependent claims which recite 'further containing' a pharmaceutical carrier are thus, indefinite; according to claims 27 and 42, the pharmaceutical carrier is either a water or a buffer.

The distinction between a sterilized saline solution and an aqueous solution containing sodium chloride is unclear. Similar is the case with sterilized buffered water and aqueous solution containing buffering agents and pH adjusting agents and sodium acetate.

The independent claims recite liposomes consisting essentially of phospholipids; claims 34 and 49 which recite non-phospholipids thus, are deemed to be indefinite. On the same basis, the dependent claims 33 and 48 which recite agents which are bound to the liposomes are indefinite since the liposomes no longer consists essentially of phospholipids, but other agents which changes the nature of the composition.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 23-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,139,871. Although the conflicting claims are not identical, they are not patentably distinct from each other because liposome sizes of 100-150 nm recited in the claims of said patent is included in instant 'greater than about 100 nm sizes; instant claims include the specific amounts of phospholipids recited in the claims of said patent.

Applicant has neither provided specific arguments nor filed a terminal disclaimer. Hence, the rejection is maintained.

Claim Rejections - 35 U.S.C. § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless --**
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

6. Claims 23-27, 29-32, 34-42, 44-47, and 49-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu (BBA, 1990).

Liu discloses liposomes of instant sizes(note the abstract, Materials and Methods, and results).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Liu teaches a non-phospholipid containing liposomes. According to applicant, Liu's liposomes are made of dioleolyl-phosphatidylethanolamine and dipalmitoylsuccinylglycerol or gangliosides which are not phospholipids. This argument is not found to be persuasive since according to instant invention, liposomes can contain non-phospholipids (page 10, line 33 et seq.). Furthermore, in instant dependent claims 34 and 49, applicant himself recites cerebrosides, dicetylphosphate, a

trimethylammonium chloride derivative and others; these are not phospholipids. Liu teaches phospholipid liposomes which also contain a lipid which is not a phospholipid just as in instant invention. With regard to applicant's arguments that Liu's liposomes are designed to deliver drugs to the cytoplasm, the examiner points out that intended use has no significance in the composition claims.

7. Claims 23-24, 26-32, 34-47, and 49-54 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 470 437.

EP teaches unilamellar liposomes having an average diameter of 100 nm containing phosphatidylcholine for the treatment of atherosclerosis (note pages 10, 11, 15 and 16 of the English translation).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that liposomes of instant invention have an average diameter of greater than about 100 nm and Hager teaches less than 100. Applicant is incorrect in stating so. Hager in Example 3 (page 13 of the translation) clearly teaches liposomes of average diameter of 129 nm. Furthermore, Hager's average size range of liposomes is 50-180 nm and instant average diameter ranges fall within the ranges in Hager.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

9. Claims 23-32, 34-47, and 49-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP cited above by itself or in view of Williams 1984 (Perspectives in Biology and Medicine).

EP does not provide specific examples for the treatment of atherosclerosis. It would however, been obvious to an artisan to use liposomes for the treatment of atherosclerosis based on the teachings of EP. EP does not specifically state that the phosphatidylcholine used should be from eggs. EP does not also specifically teach instant protocol and mode of administration. In the absence of showing unexpected results, these parameters are deemed to be obvious parameters manipulated by an artisan to obtain the best possible results. One of ordinary skill in the art would be motivated to administer the liposomes of EP by an intravenous injection, with the expectation of obtaining similar results since the reference of Williams et al teaches the administration of similar liposomes for the treatment of the same disease (note the entire article of Williams, pages 417, 418, 422, 424 and 425 in particular).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues regarding the sizes of the liposomes. These arguments have been addressed above. Applicant argues that the sizes of liposomes in Williams are small. This argument is not found to be persuasive since Williams is combined because it specifically discusses experimental studies on the effectiveness of liposomes in treating atherosclerosis and instant sizes are taught in EP.

10. Claims 33 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP cited above by itself or in view of Williams 1984, in further combination with Williams 1986 and Konigsberg (5,258,499).

What is lacking in EP and Williams 1984 is the teaching of the attachment of apoproteins on the surface of the liposomes.

Williams (1986) while disclosing a method of removal of serum cholesterol using liposomes teaches that apolipoproteins enhance the ability of phospholipid dispersions to extract cellular cholesterol in vitro and presumably enhance this ability in vivo as well. (note the abstract, Introduction, Materials and Methods and Discussion, last paragraph in particular).

The reference of Konigsberg teaches the method of attachment of proteins on the surface of the liposomes (note the abstract and claims).

The attachment of apoproteins on the surface of the liposomes would have been obvious to one of ordinary skill in the art since Williams teaches that apoproteins enhance

the cholesterol removal by liposomes and that of Konigsberg teaches the knowledge of attachment of proteins on the surface of liposomes.

11. Claims 23-27, 28-32, 34-47, and 49-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams (1984 or 1986) in view of Liu.

Williams (1984) teaches the administration of liposomes for treating atherosclerosis, but does not teach the sizes (pages 418-423). This parameter however, if different from instant invention, is deemed to be an obvious parameter manipulated by an artisan to obtain the best possible results. Instant liposome sizes are also deemed to be obvious to one of ordinary skill in the art in view of Liu's teachings that SUVs of about 120 nm have greater circulation time.

Williams (1986) disclose a method of removal of serum cholesterol using liposomes (note the abstract, Introduction, Materials and Methods and Discussion, last paragraph in particular). Although on page 185, col. 1, Williams discloses the use of 0.22 mm filter, he does not specifically teach instant sizes.

Liu teaches that small liposomes (<200 nm) remain in circulation for a longer periods (note page 348, col. 2, Results on page 350, col. 1).

To prepare liposomes of Williams (1984 or 1986) having sizes within the claimed range would have been obvious to one of ordinary skill in the art since liposomes of those sizes are able to survive the circulation system for longer periods (and hence their

enhanced cholesterol removal effect) as taught by Liu. The protocol of administration is deemed to be an obvious parameter manipulated by an artisan.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Liu teaches a non-phospholipid containing liposomes and therefore, teaches away from the invention. This argument is not found to be persuasive since according to instant invention, liposomes can contain non-phospholipids (page 10, line 33 et seq.). Liu teaches phospholipid liposomes which also contain a lipid which is not a phospholipid just as in instant invention. Furthermore, in instant dependent claims 34 and 49, applicant himself recites cerebrosides, dicetylphosphate, a trimethylammonium chloride derivative and others; these are not phospholipids. Therefore, it cannot be c considered as teaching away. It is interesting to note that in response to 112, first paragraph rejection (which is now withdrawn), applicant argues that non-phospholipids can be present in the liposomes. Applicant argues that according to Liu, the longer circulation period is not due to the size of the liposome but rather is a function of ganglioside. Applicant is incorrect in this assumption since on col. 1, page 350 Liu clearly teaches the longer circulation times of smaller liposomes which are made of DOPE and DPSG and no gangliosides. Applicant's arguments that one skilled in the art combining Williams (1984) or (1986) would formulate small liposomes composed of over 20 % non-phospholipid designed to avoid uptake Kupffer cells are not found to be persuasive since

the sizes referred to by Liu on page 350 are of average diameter of 120 nm and therefore, would behave the same way as in instant invention.

12. Claims 34 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over (EP cited above by itself or in view of Williams 1984) or (Williams (1984 or 1986) in view of Liu) as set forth above, further in view of Barenholz (4,812,314).

The primary references do not teach instant phospholipids. Such a use however, would have been obvious to one of ordinary skill in the art in view of Barenholz's teachings of the general ability of phospholipids to remove cholesterol through a variety of physiological transfer proteins (note col. 2, line 41 through col. 3, line 25). An artisan would expect at least similar removal of cholesterol by other phospholipids.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to EP, Liu, Williams have already been addressed above. Applicant argues that Barenholz teaches using a suspension of small unilamellar liposomes composed predominately of egg phosphatidylcholine for treating cellular aging by exchanging the sphingomyelin and cholesterol of biological membranes with the phosphatidylcholine of the liposomes and thus, does not remedy the deficiencies in Hager or Williams 1984 or 1986 or Liu. This argument is not found to be persuasive since Barenholz is suggestive of the ability of other phospholipids to exchange cholesterol through a variety of physiological transfer proteins.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

October 30, 2002